IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of:	Confirmation No.: 8024
Wilhelmus E. HENNINK et al.	Examiner: Blessing M. Fubara
Application No.: 09/913,967	Group Art Unit: 1618
Filed: February 21, 2000 (Int'l)	
For: STEREOCOMPLEX HYDROGELS	

BRIEF ON APPEAL

MS Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

The rejection of claims 1, 15-17, 24 and 27-31 is hereby appealed. This Brief is filed in accordance with 37 C.F.R. § 41.37.

A Notice of Appeal was filed in the present application on October 13, 2009, thus setting a date for filing the Brief of December 13, 2009. Because December 13, 2009 fell on a Sunday, this Brief is filed on the next business day, Monday, December 14, 2009. Accordingly, this Brief is timely filed.

Claims 1, 15-17, 24 and 27-31 are subject to this Appeal.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1206:

I. Real Party in Interest
II Related Appeals and Interferences
III. Status of Claims
IV. Status of Amendments
V. Summary of Claimed Subject Matter
VI. Grounds of Rejection to be Reviewed on Appeal
VII. Argument
VIII. Claims
IX. Evidence
X. Related Proceedings
Appendix A Claims
Appendix B Evidence

I. REAL PARTY IN INTEREST

The Real Party in Interest is the assignee herein, Universiteit Utrecht, having an address at Heidelberglaan 98, NL-3584 CS Utrecht, Netherlands.

II. RELATED APPEALS AND INTERFERENCES

Appellants and their representatives and assignees are unaware of any proceedings related to, which will directly affect or that would be directly affected by or have a bearing on the Board's decision in this case.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 10 claims pending in the application.

B. Current Status of Claims

1. Claims canceled: 2-14, 18-23 and 25-26.
2. Claims withdrawn from consideration but not canceled: None.
3. Claims pending: 1, 15-17, 24 and 27-31.
4. Claims allowed: None.
5. Claims rejected: 1, 15-17, 24 and 27-31.
6. Claims objected to: None.

C. Claims on Appeal

The claims on appeal are claims 1, 15-17, 24 and 27-31.

IV. STATUS OF AMENDMENTS

No amendments to the claims were proposed after final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

There are two independent claims, claims 1 and 15, from which all remaining claims on appeal depend.

Claim 1 is directed towards a hydrogel composition comprised of a mixture of a dextran polymer grafted with homo-oligomers of L-lactic acid and a dextran polymer grafted with homo-oligomers of D-lactic acid, in an aqueous system. A generic description of the claimed hydrogel compositions is provided on page 5, lines 25-30.

Claim 1 is further limited to compositions comprising dextran polymers grafted with homo-oligomers of L- and D-lactic acid, wherein the homo-oligomers have 7-25 lactic acid monomers on average, as described on page 10, lines 3-4.

The various features of independent claim 1 are supported by the specification as indicated below:

1. Hydrogel composition comprised of a mixture of (page 5, lines 31- 32)

(A) a dextran polymer (page 9, line 25) grafted with (page 9, line 26) homo-oligomers of L-lactic acid (page 11, line 1), and

(B) a dextran polymer (page 9, line 25) grafted with (page 9, line 26) homo-oligomers of D-lactic acid (page 10, line 24),

in an aqueous system (page 5, lines 33),

wherein said homo-oligomers of L-lactic acid (page 11, line 1) and said homo-oligomers of D-lactic acid (page 10, line 24) have 7-25 lactic acid monomers on average (page 10, lines 3-5).

Claim 15 is directed towards a process for preparing a hydrogel composition as claimed in claim 1. A generic description of this process is found on page 17, line 31 to page 18, line 9.

The various features of independent claim 15 are supported by the specification as indicated below:

15. Process for the preparation of a hydrogel (page 17, lines 31-32) comprising:

a) polymerizing (page 18, lines 1-4) L-lactic acid (page 5, lines 28-30), optionally in the presence of a suitable initiator (page 18, lines 1-2);

b) polymerizing (page 18, lines 1-4) D-lactic acid (page 5, lines 28-30), optionally in the presence of a suitable initiator (page 18, lines 1-2);

c) reacting the product of step a) with a suitable coupling compound (page 18, lines 5-6) and a dextran polymer (page 9, line 25) to form a dextran polymer grafted with (page 9, line 26) homo-oligomers of L-lactic acid (page 11, line 1);

d) reacting the product of step b) with a suitable coupling compound (page 18, lines 5-6) and a dextran polymer (page 9, line 25) to form a dextran polymer grafted (page 9, line 26) with homo-oligomers of D-lactic acid (page 10, line 24);

wherein said homo-oligomers of L-lactic acid (page 11, line 1) and said homo-oligomers of D-lactic acid (page 10, line 24) have 7-25 lactic acid monomers on average (page 10, lines 3-5); and

e) mixing the product of step c) and the product of step d) (page 18, line 9) in an aqueous system (page 5, line 33) to provide said hydrogel (page 5, line 31).

In addition, claim 24 is directed towards a method for drug delivery (page 4, lines 18-20) comprising administering a hydrogel composition (page 16, lines 28-30) as in claim 31, where claim 31 relates to a hydrogel as described in claim 1, further comprising an active ingredient

(page 16, lines 28-30), wherein the active ingredient is a drug to be released (page 11, lines 11-13).

The various features of claim 24 are supported by the specification as indicated below.

24. A method for drug delivery (page 4, lines 18-20) comprising administering the hydrogel composition (page 16, lines 28-30) of claim 31.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Claim 1 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Li et al., *Polymer* (1997), 38: 6197-6206 (hereinafter "Li (1997)") or Li et al., *Polymer* (1998), 39:3087-97 (hereinafter "Li (1998)").

B. Claims 1, 24 and 29-31 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Li (1998), as evidenced by Graham (U.S. Patent No. 4,814,182).

C. Claim 15-17, 27 and 28 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Li (1997) in view of Jarrett (U.S. Patent No. 4,788,979) or Bays (U.S. Patent No. 4,650,488).

VII. ARGUMENT

A. Claim 1 is Not Rendered Obvious by Li (1997) or Li (1998), alone or in combination

1. Brief Summary of Pertinent Disclosure of Li (1997) and Li (1998)

Li (1997) discloses the preparation of biodegradable brush-like graft polymers of dextran sodium sulphate (DSS) and diethylaminoethyl dextran chloride (DEAED) grafted with racemic D,L-polylactic acid (PLA) or with poly(D,L-lactide-co-glycolic acid) (PLG). The polymers are suggested to be useful as biodegradable parenteral drug delivery systems. Li (1997) suggests

that the D,L-lactide grafted polymers are not soluble in water (i.e., the PLA grafts seem to be of such size that they control solubility over the dextran-type backbones), noting that the polymers are soluble in organic solvents (page 6199, col. 2, second paragragh) and are obtained in high yield after "exhaustive extraction with water." *Id.* Li (1998) discloses the preparation of microspheres of the previously prepared polymers using a water/oil/water double-emulsion method. Degradation and drug release from the microspheres thus obtained is also disclosed.

2. Summary of the Examiner's Rejection Reasoning

The Examiner acknowledges that neither Li (1997) nor Li (1998) disclose combination of dextran polymers separately grafted with homo-oligomers of L- and D-lactic acid. Nevertheless, the Examiner asserts the composition formed by mixing the separate L- and D-lactide grafted dextrans reads on the D,L-lactide grafted dextran disclosed in both of the Li references because "claim 1 does not indicate any special ratios of the L-lactide dextran to the D-lactide dextran that may have provided some difference between the claims and the disclosed." Regarding the limitation that the homo-oligomers of L- and D-lactic acid have 7-25 lactic acid monomers on average, the Examiner takes the position that one of skill in the art would incorporate the appropriate number of lactide monomers to obtain the desired release properties. The Examiner asserts that, in view of the use of the open transitional phrase 'comprising' in claim 1, "the D,L-lactide grafted form of dextran meets the L-lactide and D-lactide grafted dextran. In the absence of unexpected result, a composition that comprises D,L-lactide grafted dextran that is a combination of L-lactide grafted dextran and D-lactide grafted dextran is not inventive over a D,L-lactide grafted dextran."

3. Response to the Examiner's Rejection

The Office has failed to establish that claim 1 is a *prima facie* obvious over Li (1997) or Li (1998), alone or in combination. While the strict teaching - suggestion - motivation (TSM) test was rejected by the Supreme Court in *KSR v. Teleflex*, there still must be an "articulated reasoning with some rational underpinning to support the legal conclusion" of obviousness. *KSR International Co. v. Teleflex, Inc.*, 82 U.S.P.Q.2d 1385, at 1396 (S. Ct. 2007). Determining if there is an articulated reason requires analysis of a number of factors, including, e.g., whether there is evidence of teaching away and whether there is a reasonable expectation of success. Critical elements of the invention as a whole which clearly distinguish the entire invention from the prior art references cannot be ignored. *Panduit Corp. v. Dennison Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). In order for a combination of documents to defeat patentability, the Court in *KSR* held that the practitioner must have some reason to combine the elements in the way the claimed new invention does.

Claim 1 is directed towards a hydrogel composition comprised of a mixture of a dextran polymer grafted with homo-oligomers of L-lactic acid and a dextran polymer grafted with homo-oligomers of D-lactic acid in an aqueous system. (Specification at, e.g., page 9, lines 24-27, and in Examples 1 and 2.) As described in the specification, mixing water soluble or dispersible polymers (e.g., dextrans) grafted with oligomers formed from chiral monomers having opposite chirality results in non-covalent, physical interactions between the grafts, providing a stereocomplex gel structure. (Specification, at page 5, lines 10-15.)

The instant inventors were the first to discover the formation of stereocomplexes "by mixing aqueous solutions/dispersions of a water-soluble or dispersible polymer (e.g., dextran) to which oligomers of opposite chirality are substituted (preferably grafted)." See Declaration of

Wilhelmus Everhardus Hennink, submitted with the response of January 24, 2005 (hereinafter "Hennink Declaration I"), at paragraph 3. Formation of hydrogels can be assessed using rheologic behavior to determine the presence of physical interactions (i.e., stereocomplex formation). (Specification, at page 18, lines 16-20 and Examples 3 and 4).

As the Examiner has acknowledged, Li (1997) and Li (1998) do not disclose combination of dextran polymers separately grafted with homo-oligomers of D- and L-lactic acid. In fact, neither Li (1997) nor Li (1998) discloses or otherwise suggests the formation of hydrogels at all, and neither reference discloses or suggests the formation of stereocomplexes between D-lactic acid homo-oligomers and L-lactic acid homo-oligomers. Thus, whether considered alone or in combination, Li (1997) and Li (1998) fail to provide any guidance that would lead one of skill in the art to prepare hydrogels formed by stereocomplex interactions between homo-oligomers of D- and L-lactic acid on separate dextran strands, as claimed.

As evidenced by the Declaration of Wilhelmus Everhardus Hennink submitted with the response of April 27, 2006 (hereinafter "Hennink Declaration II"), hydrogels are formed from colloids in which the disperse, or colloidal phase has combined with the continuous phase (water) to produce a jellylike product, and generally contain from about 20 to more than 99 weight % water. See Hennink Declaration II, at paragraph 3. The suggestion in Li (1997) that the D,L-lactide grafted polymers are water insoluble teaches away from the use of such polymers for the formation of hydrogels, and in view of this disclosure, one of skill in the art would not reasonably have concluded that such polymers would be useful for the formation of hydrogels.

In addition, the Examiner has improperly disregarded the express claim limitation that the homo-oligomers of D- and L-lactic acid have 7-25 monomers on average. The use of the open transitional language 'comprising' does not negate this requirement. As indicated in the

specification, the degree of polymerization (DP) is selected so that the grafts are long enough to physically interact to form a hydrogel without compromising water solubility or dispersibility. (Specification, page 9, lines 16-24). The polymers of Li (1997) and Li (1998) do not contain chiral homo-oligomers of opposite chirality that can physically interact to form hydrogels, as in the claimed compositions. Thus, there is no basis to conclude that optimization of the release properties of Li's microspheres would necessarily result in the preparation of polymers grafted with oligomers having 7-25 monomers on average, as claimed.

Moreover, the Office has failed to provide a clearly articulated rationale that would have led one of ordinary skill in the art to combine and/or modify the teachings of the cited references to achieve the present invention.

As discussed above, Li (1997) and Li (1998) disclose the preparation of dextran grafted with oligomers of D,L-lactic acid, i.e., the racemic mixture. In order for one of skill in the art to arrive at the instant invention from the disclosures of Li et al., the skilled person would need to take the following steps: (1) separate D- and L-lactate; (2) use only or at least predominantly D-lactic acid to prepare dextran grafted with homo-oligomers of D-lactic acid; (3) use only or at least predominantly L-lactic acid to prepare dextran grafted with homo-oligomers of L-lactic acid; and (4) bring the D- and L-grafted dextran chains together in an aqueous environment. In the absence of any guidance or other rationale that would suggest that the product achieved via this process would have some advantageous properties, one of skill in the art would simply have no motivation to undertake each of the four steps required to practice the invention as claimed.

As previously noted by the Appellants, separation of D,L-lactide into the individual enantiomers is a difficult and expensive process, and one of skill in the art would not

automatically undertake the separation of the racemate without some clear reason to do so, which the Office has not provided.

Even assuming for the sake of argument that one of ordinary skill decided for some reason to use oligomers of either pure D- or pure L-lactic acid, the Examiner has pointed to nothing in the cited art that would lead the artisan to prepare dextran polymers *separately* grafted with homo-oligomers of D- and L-lactic acid having 7-25 monomers on average, and then to *combine* these polymers *in an aqueous system* in the way that the claimed invention does to achieve the present result. Thus, the present invention requires a separate inventive step to utilize a polymer grafted with L-lactide homo-oligomers and a polymer grafted with D-lactide homo-oligomers in combination in an aqueous system, which is neither taught nor otherwise suggested by the cited art, alone or in combination.

B. Claims 1, 24 and 29-31 are Not Rendered Obvious by Li (1998), alone or as evidenced by Graham

1. Brief Summary of Pertinent Disclosures of Li (1998) and Graham

As discussed above, Li (1998) discloses the preparation of microspheres of dextran polymers grafted with D,L-lactide, and suggests that such microspheres may be useful as biodegradable parental-depot systems. Graham discloses controlled release devices comprising a hydrogel incorporating an active substance, and an aqueous impermeable layer that provides controlled release of the active substance. Graham discloses dextran as a cross-linkable biopolymer useful to form hydrogels, but does not mention lactide-grafted polymers at all.

2. Summary of the Examiner's Rejection Reasoning

The Examiner asserts that Li (1998) prepare lactide grafted dextran as microspheres, allegedly meeting the limitations of dependent claim 29. The Examiner further asserts that Li (1998) disclose that proteins such as BSA can be released from grafted polymers, allegedly meeting the limitations of dependent claims 30 and 31. The Examiner acknowledges that Li (1998) does not disclose that their microsphere formulation is a hydrogel. Nevertheless, the Examiner asserts that lactide and dextran hydrogels are known in the art, and thus concludes that one of skill in the art would formulate the composition as a hydrogel, allegedly as evidenced by Graham.

3. Response to the Examiner's Rejection

With regard to dependent claims 29-31, the Appellants note that each of these claims relates to a hydrogel composition as in claim 1. Claim 24 relates to a method of drug delivery comprising administering a hydrogel composition, further comprising a drug to be released as an active ingredient. Thus, as a threshold matter, the lack of a *prima facie* case of obviousness for claim 1 over Li (1998), as discussed in detail above, renders the present rejections of claims 24 and 29-31 improper. While the specification discloses that the claimed hydrogels can be formed as microspheres (as in claim 29; Specification, page 16, line 32 to page 17, line 8), this does not provide evidence for Examiner's apparent unsupported conclusion that the converse must be true, i.e., that all microspheres can be formed as hydrogels.

As already discussed, Li (1998) relates to biodegradable microsphere formulations which the Examiner has acknowledged are <u>not</u> hydrogel compositions, as required by the instant claims. The Office has failed to provide a clearly articulated rationale that would have led one of

ordinary skill in the art to modify the microspheres of Li (1998) to form hydrogels at all, and in particular, to make the specific modifications necessary to achieve the instant invention.

Graham is cited as allegedly providing evidence that lactide and dextran hydrogels are known in the art, and by inference, that this somehow provides a rationale for one of skill in the art to modify the microspheres of Li (1998) to provide hydrogels. While Graham lists dextran as a cross-linkable biopolymer that can be used to form hydrogels, the reference does not mention lactide grafted polymers at all. In addition, Graham discloses that chemically cross-linked (i.e., covalently linked) synthetic hydrophilic polymers are preferred. (See Graham et al., col. 2, lines 52-56.) Thus, taken as a whole, Graham provides no guidance that would lead one of skill in the art to modify the D,L-lactide grafted dextrans of Li (1998) to prepare dextran polymers separately grafted with homo-oligomers of D- or L-lactic acid, or to combine such polymers in an aqueous system as required to achieve the instant invention.

Appellants respectfully submit that the disclosure by Graham et al. that covalently cross-linked hydrogels have been prepared from unrelated polymeric compositions provides neither an incentive nor a reasonable expectation of success that would have led one of ordinary skill to modify the teachings of Li (1998) in the manner necessary to achieve the present invention.

In addition, nothing in Graham et al. alters the teachings of Li (1997) that D,L-lactide grafted dextran polymers are water insoluble and thus unlikely to be useful for the preparation of hydrogels, as discussed in more detail below.

C. Claims 15-17, 27 and 28 are Not Rendered Obvious by Li (1997) in combination with Jarrett or Bays

1. Brief Summary of Pertinent Disclosures of Li (1997), Jarrett and Bays

Li (1997) discloses the preparation of brush-like graft polymers from poly(D,L-lactide) or poly(D,L-lactide-co-glycolide) and charge-modified dextran polymers. Li's polymers were prepared by heating the dextran polymer and, for example, racemic poly(D,L-lactide) in the presence of stannous octanoate to polymerize, then dissolving in methylene chloride and washing with water to remove unreacted polymer. See Li (1997) at page 6198, col. 2. The resulting product is not a hydrogel, but rather a polymer that is soluble in organic solvents. See Li (1997) at page 6199, col. 2, second paragraph: "The purified polymers are soluble in dichloromethane."

Further, Li (1997) discloses that high yields (>90%) are obtained after "residual amounts of unreacted DSS are removed *by exhaustive extraction with water* to obtain pure polymers." See Li (1997) at 6199, col. 2, second paragraph (emphasis added). Appellants consider it clear that if the grafted polymers of Li were water soluble, they would not be obtainable in high yield after exhaustive aqueous extraction. In addition, Li (1998) disclose that in the DSS- and DEAED-PLG polymers, "[t]he backbones *become water soluble* when most of the branches have been cleaved by hydrolysis." See Li (1998), sentence bridging pages 3090-3091 (emphasis added). Taken together, these statements support the conclusion that the D,L-lactide grafted polymers prepared by Li are <u>not</u> soluble in water, i.e., the PLA grafts seem to be of such size that they control solubility over the dextran-type backbones.

Bays discloses a prosthetic device (i.e., an ear tube) formed from a biodegradable material, which may include poly(D,L-lactide), or lactide/glycolide copolymers formed by polymerization of the appropriate monomers using lauryl alcohol as a polymerization initiator.

Jarrett discloses synthesis of a a block copolymer of caprolactone and lactide or glycolide, using lauryl alcohol as an initiator.

None of the cited references discloses or otherwise suggests the formation of hydrogels.

2. Summary of the Examiner's Rejection Reasoning

The Examiner asserts that Li (1997) discloses preparation of D,L-lactide grafted dextran and suggests that molecules such as peptides and proteins can be delivered by lactide polymers, allegedly meeting the limitations of claim 27 and 28. The Examiner states that one of skill in the art would have a reasonable expectation that dextran grafted with the D,L-lactide or by combining the D- or L-lactide grafted forms "would provide the anticipated in vitro degradation or the polymer or in vitro degradation and controlled releases of hydrophilic molecules."

The Examiner acknowledges that Li (1997) does not disclose the use of initiators, but cites Bays (U.S. Patent No. 4,650,488) and Jarrett (U.S. Patent No. 4,788,979) as evidence that lauryl alcohol is a known polymerization initiator, allegedly meeting the limitation of the initiator in claims 15 and 16. Thus, the Examiner concludes that one of skill in the art would have a reasonable expectation that lauryl alcohol would initiate the polymerization reaction to produce lactide grafted dextrans.

3. Response to the Examiner's Rejection

As discussed above, Li (1997) fails to disclose the preparation of a hydrogel composition, as claimed in independent claim 15 and claims 16, 17, 27 and 28 that depend thereon. At best, Li (1997) discloses a process for the preparation of a lactide-grafted dextran polymer which, with the benefit of the Appellant's disclosure, could potentially be used to prepare hydrogels. However, this is not the Appellants invention, which requires not only the preparation of dextran polymers separately grafted with chiral homo-oligomers of opposite chirality, but the mixing of

these polymers in an aqueous system. These steps of the claimed process are neither taught nor otherwise suggested by the cited art.

With regard to the combination of Li (1997) with either Jarrett or Bays, neither of these references addresses the fundamental deficiencies in the Office's *prima facie* case over Li (1997) alone. The patentability of claim 15-17 and 27-28 is not predicated on the use of a polymerization initiator, which is well-known in the art. The Examiner had pointed to nothing in Li (1997), alone or in combination with Bays or Jarrett, that would lead one of skill in the art to practice the invention as claimed.

In view of the disclosure by Li (1997) suggesting that their D,L-lactide grafted dextran polymers are not water soluble, Appellants submit that one of skill in the art would not have had either a motivation or a reasonable expectation of success that dextran grafted with either D- or L-lactic acid homo-oligomers alone would be useful to prepare hydrogel compositions, which as described above typically contain from about 20 to 99 weight percent water. Moreover, Li (1997) would certainly not have provided one of skill in the art with a reasonable expectation that the combination of dextran polymers separately grafted with homo-oligomers of D-lactic acid and L-lactic acid in an aqueous environment would be useful to provide hydrogel compositions, via stereocomplex formation between polymer strands bearing homo-oligomers having complementary (i.e., opposite) chirality.

D. Evidence of unexpected results rebuts any *prima facie* case of obviousness

Because the Office has failed to establish a *prima facie* case of obviousness, the Appellants have no burden to submit rebuttal evidence. Nevertheless, a significant amount of evidence supporting the unexpectedly beneficial aspects of the claimed invention is already on the record.

As described in the specification, the controlled release properties of the claimed hydrogel compositions can be fine-tuned by varying the degree of polymerization (DP) and/or degree of substitution (DS). (Specification, page 10, lines 6-10.) The claimed hydrogels also overcome the disadvantages of delivery systems obtained using biodegradable polymers in microspheres, including, e.g., the use of organic solvents to encapsulate proteins in the microspheres, the acidic products formed during degradation, and the difficulty in controlling protein release from these systems. (Specification, page 3, lines 10-20.) In addition, the claimed hydrogels, which are formed via non-covalent physical interactions between the chiral graft oligomers, avoid the use of toxic or reactive chemical agents required for cross-linking, which may be incompatible with proteins or in vivo applications. (Specification, page 3, lines 24-35.)

E. Conclusion

The present invention provides stereocomplex hydrogel compositions and processes for preparing such compositions, as well as method of drug delivery using such hydrogel compositions. The cited art fails to disclose or otherwise suggest that non-covalently cross-linked hydrogel compositions could be formed by mixing aqueous solutions/dispersions of water-soluble or dispersible polymers (e.g., dextrans) grafted with chiral oligomers having opposite chirality.

The cited art, alone or in combination, simply provides no guidance that would lead to the preparation of the invention as claimed, and therefore does not provide one of ordinary skill in the art with either a reasonable expectation of success or any motivation or other rationale to practice the instantly claimed invention.

VIII. CLAIMS APPENDIX

An appendix containing a copy of the claims as currently pending is attached hereto as Appendix A.

IX. EVIDENCE APPENDIX

An appendix containing the following documents already of record in this case is attached hereto as Appendix B:

1. Li et al., *Polymer* (1997), **38**: 6197-6206.
2. Li et al., *Polymer* (1998), **39**:3087-97.
3. U.S. Patent No. 4,788,979, to Jarrett et al.
4. U.S. Patent No. 4,650,488, to Bays et al.
5. U.S. Patent No. 4,814,182, to Graham et al.
6. Declaration of Wilhelmus Everhardus Hennink (submitted with the Response filed January 24, 2005)
7. Short Curriculum Vitae and publication list of Wilhelmus E. Hennink (submitted with the Response filed January 24, 2005)
8. Declaration of Wilhelmus Everhardus Hennink (submitted with the Response filed April 27, 2006), and Exhibits 1-3 submitted therewith
    a. Exhibit 1, McGraw-Hill Dictionary of Scientific and Technical Terms
    b. Exhibit 2, schematic representation of covalently crosslinked hydrogels
    c. Exhibit 3, schematic representation of non-covalently crosslinked hydrogels of the instant invention

X. RELATED PROCEEDINGS APPENDIX

There are no related proceedings, therefore no Appendix is included.

The Assistant Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.17 that may be required by this Brief, or to credit any overpayment, to **Deposit Account No. 03-1952**.

Respectfully submitted,

Dated: December 14, 2009

By: / Leslie A. Robinson /
Leslie A. Robinson
Registration No. 54,403

Morrison & Foerster LLP
12531 High Bluff Drive
Suite 100
San Diego, California 92130
Telephone: (858) 314-7692
Facsimile: (858) 720-5125

APPENDIX A

Complete Listing of the Claims, including Claims Involved in the Appeal of Application Serial 09/913,967:

1. (previously presented): Hydrogel composition comprised of a mixture of

(A) a dextran polymer grafted with homo-oligomers of L-lactic acid, and

(B) a dextran polymer grafted with homo-oligomers of D-lactic acid,

in an aqueous system,

wherein said homo-oligomers of L-lactic acid and said homo-oligomers of D-lactic acid have 7-25 lactic acid monomers on average.

2-14. (canceled)

15. (previously presented): Process for the preparation of a hydrogel comprising:

a) polymerizing L-lactic acid, optionally in the presence of a suitable initiator;

b) polymerizing D-lactic acid, optionally in the presence of a suitable initiator;

c) reacting the product of step a) with a suitable coupling compound and a dextran polymer to form a dextran polymer grafted with homo-oligomers of L-lactic acid;

d) reacting the product of step b) with a suitable coupling compound and a dextran polymer to form a dextran polymer grafted with homo-oligomers of D-lactic acid;

wherein said homo-oligomers of L-lactic acid and said homo-oligomers of D-lactic acid have 7-25 lactic acid monomers on average; and

e) mixing the product of step c) and the product of step d) in an aqueous system to provide said hydrogel.

16. (previously presented): Process according to claim 15, said suitable initiator comprising a primary or secondary hydroxyl group.

17. (previously presented): Process according to claim 15, wherein an active ingredient is added prior to or during step e).

18-23. (canceled)

24. (previously presented): A method for drug delivery comprising administering the hydrogel composition of claim 31.

25-26. (canceled)

27. (previously presented): Process according to claim 17, wherein the active ingredient is a drug to be released.

28. (previously presented): Process according to claim 27, wherein the drug to be released is selected from proteins and proteinaceous products.

29. (previously presented): Hydrogel composition according to claim 1, wherein the hydrogel is formed in microspheres.

30. (previously presented): Hydrogel composition according to claim 1, further comprising an active ingredient.

31. (previously presented): Hydrogel composition according to claim 30, wherein the active ingredient is a drug to be released.

APPENDIX B

This appendix contains the following evidentiary material already of record:

1. Li et al., *Polymer* (1997), **38**: 6197-6206.
2. Li et al., *Polymer* (1998), **39**:3087-97.
3. U.S. Patent No. 4,788,979, to Jarrett et al.
4. U.S. Patent No. 4,650,488, to Bays et al.
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    a. Exhibit 1, McGraw-Hill Dictionary of Scientific and Technical Terms
    b. Exhibit 2, schematic representation of covalently crosslinked hydrogels
    c. Exhibit 3, schematic representation of non-covalently crosslinked hydrogels of the instant invention